The "Knife-Cut Sign" Revisited

A Distinctive Presentation of Linear Erosive Herpes Simplex Virus Infection in Immunocompromised Patients

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ABSTRACT

Background: The "knife-cut sign" is a distinctive presentation of linear erosive herpes simplex virus infection in immunocompromised patients. **Purpose:** To describe a man whose herpes simplex virus infection-related skin lesions demonstrated the "knife-cut sign" and to review the characteristics of reported immunosuppressed individuals with "knife-cut" cutaneous herpes simplex virus lesions. **Methods:** A man with multiple myeloma and post-stem cell transplant cutaneous graft-versus-host disease managed with systemic prednisone and sirolimus developed disseminated cutaneous herpes simplex virus infection with virus-associated linear ulcers of the inguinal folds and the area between his ear and scalp; the lesions at both sites had a distinctive "knife-cut" appearance. Using the PubMed database, an extensive literature search was performed on herpes simplex virus, immunocompromised patient, and "knife-cut sign". **Results:** Herpes simplex virus infection-associated skin lesions that demonstrate the "knife-cut sign" present in patients who are immunosuppressed secondary to either an underlying medical condition or a systemic therapy or both. The distinctive virus-related cutaneous lesions appear as linear ulcers and fissures in intertriginous areas, such as the folds in the inguinal area, the vulva, and the abdomen; in addition, other sites include beneath the breast, within the gluteal cleft, and the area between the ear and the scalp. Not only herpes simplex virus-2, but also herpes simplex virus-1 has been observed as the causative viral serotype; indeed, herpes simplex virus-1 has been associated with genital and inframammary lesions in addition to those above the neck. Direct fluorescent antibody testing is a rapid method for confirming the clinically suspected viral infection; however, since false-negative direct fluorescent antibody testing occurred in some of the patients, it may be prudent to also perform viral cultures and possibly lesional skin biopsies to establish the diagnosis. The herpes simplex virus infection-related skin lesions clinically improve once systemic antiviral therapy is initiated. **Conclusion:** In immunosuppressed individuals, the "knife-cut sign" is a distinctive presentation of cutaneous linear erosive herpes simplex virus infection. Recognition of the linear ulcers in intertriginous areas and body folds should prompt the clinician to consider herpes simplex virus infection-associated skin lesions in an immunocompromised patient and to initiate systemic antiviral treatment while awaiting the results of laboratory evaluation to confirm the suspected diagnosis. (*J Clin Aesthet Dermatol.* 2015;8(10):38–42.)

Herpes simplex virus (HSV) is a linear, enveloped double-stranded DNA virus; infection is often associated with oral labial lesions from HSV type 1 (HSV-1) and genital lesions from HSV type 2 (HSV-2).[1–3] However, in immunocompromised patients HSV-1 and HSV-2 can present in different locations with variable morphologies.[4,5] An immunosuppressed man with disseminated HSV-1 infection who presented with multiple virus-related skin lesions—including linear ulcers in the inguinal folds and the curved fold in the supra-auricular area between the ears and scalp—is described, and the features of previously reported immunocompromised patients with HSV infection-associated linear erosive lesions demonstrating the "knife-cut sign" are reviewed.

CASE REPORT

An immunosuppressed 57-year-old man with a history of multiple myeloma was hospitalized for fever, neutropenia, and skin lesions on his head, face, groin, and legs in October 2013. He had received several stem cell transplants and his clinical course has subsequently been complicated by fungal (aspergillus), mycobacterial (*Mycobacteria Kansasii*), and viral (recurrent oral HSV and reactivitation of Ebstein-Barr virus and

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cytomegalovirus) infections. He also developed cutaneous graft-versus-host disease, which has been chronically managed with varying dosages of prednisone and sirolimus in addition to extracorporeal photophoresis and rituxan. He had no personal or family history of Crohn's disease.

A month earlier, he had been hospitalized for an exacerbation of his cutaneous graft-versus-host disease. An eczematous auricular dermatitis with concurrent *Pseudomonas aeruginosa* infection was treated with intravenous imipenem-cilastatin and subsequently oral ciprofloxacin. A HSV-1 culture-positive lateral tongue ulcer was treated by increasing the dosage and frequency of oral valacyclovir.

Cutaneous examination showed diffuse erythroderma. Crusted ulcers were present on the face—malar cheeks, columella of the nose and extending to the nasal tip, and oral commisures. Annular erosions were present on the shoulders, back, and legs. Large linear ulcers, similar in appearance to a 'knife-cut', were present in both inguinal folds; sharply demarcated ulcers were also present on the suprapubic area, scrotum, and penile shaft (Figure 1). Linear ulcers, again similar in appearance to a "knife-cut," were present bilaterally in the curved supra-auricular fold between the external ear and the scalp (Figure 2).

The clinical differential for the skin lesions included ecthyma gangrenosum (disseminated *Pseudomonas aeruginosa* infection) or disseminated HSV infection or both. The patient was empirically treated with intravenous antibiotic (meropenen and vancomycin) and antiviral (acyclovir) therapy. Subsequently, evaluation of the specimens from the ulcer base for direct fluorescent antibody test and for viral culture were both positive for HSV-1. Skin biopsy of the ulcer showed multinucleated

Figure 1. Distant (A) and closer (B) views of the right inguinal fold herpes simplex virus type 1-positive "knife-cut" linear ulcer in an immunocompromised man with multiple myeloma following several stem cell transplants and receiving systemic immunosuppressive therapy for cutaneous graft-versus-host disease. Additional ulcers can also be observed in the suprapubic area and scrotum.

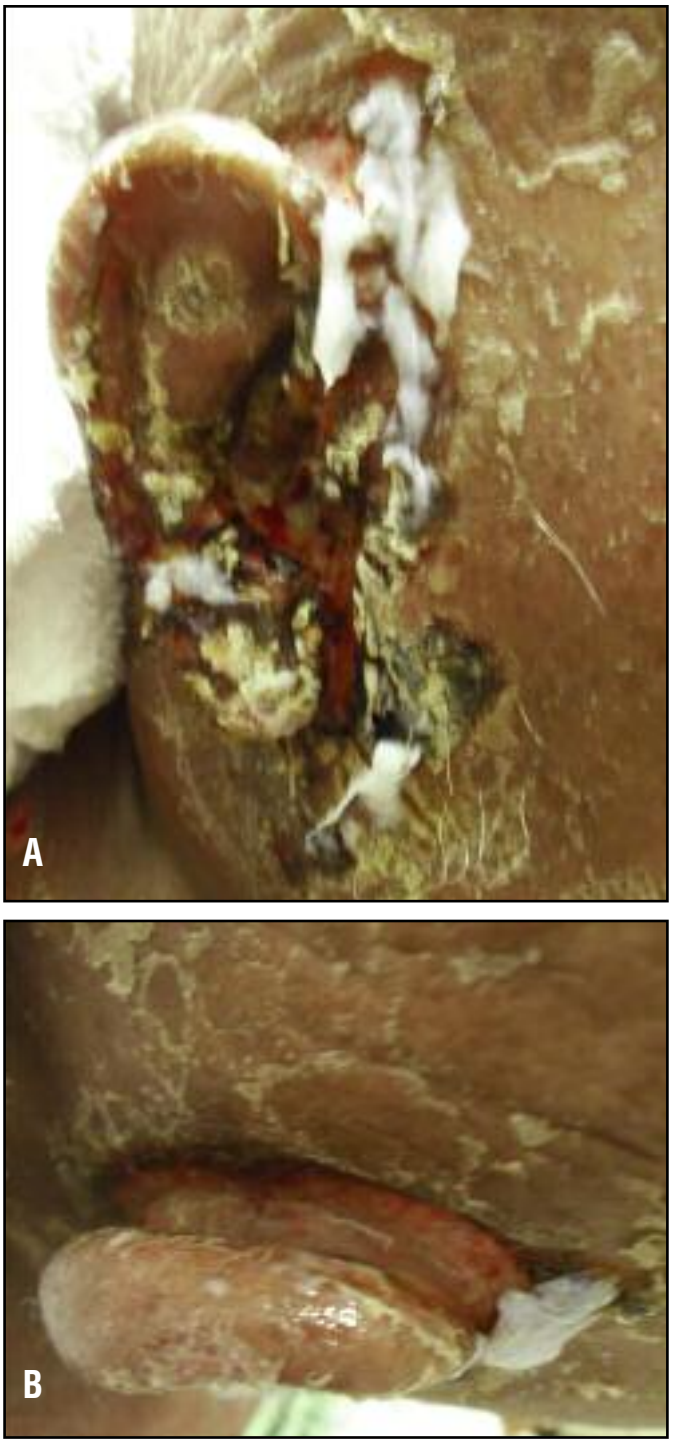

Figure 2. The distant view (A) shows the anterior surface of the patient's right external ear and adjacent preauricular face. Numerous herpes simplex virus type-1 ulcers and crusted erosions are present; silver sulfadiazine 1% cream has been applied to the area. Medial to the location where the superior helical rim attaches to the face, the proximal aspect of the patient's linear ulcer with a "knife-cut" appearance can be seen. The closer view (B) is from above the patient's head and shows the superior helix of his right ear, an ulceration, and the right temporal scalp; his occipital scalp rests against the white cloth. A linear ulcer caused by herpes simplex virus type-1, with a "knife-cut" appearance, is present in the curved supra-auricular fold between the right external ear and the scalp.

epidermal giant cells with marginated chromatin and molding of nuclei consistent with a herpes virus infection. Bacterial, fungal, and mycobacterial cultures obtained from the skin biopsy were negative.

Review of the patient's prior viral cultures from January 2013 showed acyclovir resistance HSV. Therefore, his antiviral treatment was changed to intravenous foscarnet. All of his linear erosive HSV-associated viral lesions—including the ulcers on his inguinal folds and on the curved supra-auricular folds—progressively improved during the next 10 to 14 days.

DISCUSSION

HSV infection can result in distinctive virus-associated lesions in immunocompromised patients. Grossman's geometric glossitis, originally described in 1993,[6] refers to the unique presentation of extremely tender dorsal tongue fissures in a striking longitudinal, cross-hatched, or branched geometric pattern secondary to HSV-1 infection in individuals with immunosuppression secondary to cancer,[7] cardiac transplant,[8] or human immunodeficiency virus infection.[6,8] More recently, a distinctive pattern of linear erosive HSV infection in immunocompromised patients has been observed—the "knife-cut sign."[9,10]

The term "knife-cut" was originally used to describe not only endoscopy findings, but also clinical features observed in patients with Crohn's disease. Initially, the phrase referred to the linear fissures noted on colonoscopy.[9–11] Subsequently, "knife-cut" became the morphologic term for the vulvar skin lesions in women with metastatic Crohn's disease—a variant of the condition in which cutaneous granulomatous reactions usually occur in flexures that are separated by normal skin from the affected areas of the gastrointestinal tract.[9–13] Specifically, the fissures and deep linear ulcerations in women with vulvar Crohn's disease would most often present in the interlabial folds and at the lateral edge of the hair-bearing labia majora; the vulvar lesions had a characteristic "knife-cut" appearance.[6,14]

Cutaneous HSV infection lesions presenting with ulceration of skin fissures have been observed in the abdominal, infra-abdominal, and inframammary skin folds, the interlabial and the gluteal cleft, and the inguinal crease of immunocompromised patients.[9,10] The morphology of the viral skin lesions is similar—albeit more extensive and exaggerated—to that described in women with metastatic Crohn's disease of the vulva. Therefore, investigators have referred to this distinctive presentation of linear erosive HSV infection in immunocompromised patients as the "knife-cut sign."[9,10]

Including the patient in this report, HSV infection-associated linear erosive skin lesions demonstrating the "knife-cut sign" have been observed in five immunocompromised patients (Table 1).[9,10] All of the patients had chronic medical conditions that compromised their immunity; in addition, three of the individuals were receiving systemic corticosteroids. Direct fluorescent antibody testing rapidly established

TABLE 1. Characteristics of patients with "knife-cut sign" cutaneous HSV infection lesions

CASE	AGE (in years) RACE SEX	PREDISPOSING CONDITIONS	ITx	DIAGNOSIS of HVI	HSV SEROTYPE	KNIFE-CUT LESION LOCATIONS	OTHER HSVI SITES	TREATMENT	RESULT OF TREATMENT	REFERENCE
1	22 Afican American Female	Sap SLE	HC, Pred (x 2yr)	Dfa- VC+	HSV-2	IF (Bi), VF	–	PO Acy[a]	LtF	9, case 2
2	42 Afican American Female	AS, Cal, ESRD	HD	Dfa+	HSV-1	BB (L)	–	Top Acy[b]	D	9, case 1
3	53 Not stated Female	SBP, TB	–	Bx +[c] Dfa - VC -	HVI	IAF, IF (Bi)	–	PO Val[d]	CI[e]	9, case 3
4	57 Hispanic Male	GVHD, MM	Pred, Sir	Bx+[f] Dfa+ VC+	HSV-1	IF (Bi), SA	Ba, Fa, Le, Mo, No, Sh	IV Acy, IV Fos	CI[g]	Current report
5	66 Not stated Female	AF, AVM, DRESS LO, Se, St	Mpred	Dfa+ VC+	HSV-1	AbF, GC, IF (Bi), ILS	–	IV Acy	CH	10

Abbreviations: AbF, abdominal fold; Acy, acyclovir; AF, atrial fibrillation; AS, Asherson's syndrome (catastrophic antiphospholipid antibody syndrome); AVM, arteriovenous malformation; Ba, back; BB, beneath breast; Bi, bilateral; CR, current report; Bx, biopsy; Cal, calciphylaxis; CH, complete healing; CI, clinical improvement; D, died (4 days after initiation of therapy); Dfa, direct fluorescence antibody test; DRESS, drug rash with eosinophilia and systemic symptoms; ESRD, end stage renal disease; Fa, face; Fos, foscarnet; GC, gluteal cleft; GVHD, cutaneous graft-versus-host disease; HC, hydroxychloroquine (oral); HD, hemodialysis; HSV, herpes simplex virus; HSV-1, herpes simples virus type 1; HSV-2, herpes simplex virus type 2; HSVI, herpes simplex virus infection; HVI, herpes virus infection; IAF, infra-abdominal fold; IF, inguinal fold; ILS, interlabial sulcus; ITx, immunosuppressive treatment; L, left; Le, legs; LO, lumbar osteomyelitis (with disc-space cultures positive for methicillin-resistant Staphylococcus aureus and Clostridium paraputrificum; LtF, lost to follow-up; MM, multiple myeloma; Mo, mouth; Mpred, methylprednisolone (intravenous); No, nose; PO, oral; Pred, prednisone (oral); SAP, *Staphylococcus auerus* pustulosis; SA, supra-auricular curved fold between the external ear and the scalp; SBP, spontaneous bacterial peritonitis; Se, seizures (progressing to status epilepticus); Sero, serotype; Sh, shoulders; Sir, sirolimus; SLE, systemic lupus erythematosus; St, stroke; TB, pulmonary and peritoneal tuberculosis, incompletely treated because of medication-induced hepatitis; Top, topical; Val, valacyclovir; VC, viral culture; VF, vaginal fissures; yr, years; -, negative; +, positive.

[a]The dose of acyclovir was not stated.

[b]The acyclovir was applied four times daily for four days.

[c]The tissue biopsy specimen from the lesion showed multinucleated giant cells, consistent with the diagnosis of herpes virus infection.

[d]The patient received 1g of oral valacyclovir 3 times daily for 3 weeks.

[e]Clinical improvement was noted after 4 days of antiviral treatment.

[f]The skin biopsy of the ulcer showed multinucleated epidermal giant cells with marginated chromatin and molding of nuclei consistent with a herpes virus infection.

[g]Initial antiviral therapy was intravenous acyclovir at 10mg/kg every 8 hours; however, prior viral cultures showed acyclovir resistance HSV. His antiviral treatment was changed to intravenous foscarnet 45mg/kg every 8 hours. All of his HSV-associated erosions, annular—irregularly bordered—ulcers, deep longitudal inguinal fold ulcers and postauricular linear fissures progressively improved during the next 10 to 14 days.

the diagnosis of HSV infection in three of the patients; the diagnosis was confirmed in the two patients with false-negative direct fluorescent antibody testing by either a positive viral culture for HSV or evaluation of the lesional skin biopsy that demonstrated pathologic changes of herpes virus infection.[15] An HSV-2 serotype was observed in only one of the patients whose virus-related vaginal fissures and inguinal fold longitudinal ulcers had the "knife-cut sign." However, the herpes virus infection-associated longitudinal ulcers below their neck had HSV-1 serotype infection in at least three of the other four patients.[16]

HSV infection-associated linear ulcers with the "knife-cut sign" were most commonly observed bilaterally in the inguinal folds (4 patients). Vulvar (vaginal fold and interlabial sulcus) and abdominal or infra-abdominal fold ulcers were each observed in two patients. Other intertriginous areas or body folds, such as beneath the breast, between the ear and the scalp, and within the gluteal cleft were each affected in one patient. The

currently reported patient had disseminated cutaneous HSV infection; however, three of the other four patients had HSV infection skin lesions at more than one location.

All of the patients received antiviral therapy. One patient only received four days of topical acyclovir before expiring and another patient was started on oral acyclovir and lost to follow-up. The women treated with either intravenous acyclovir or oral valacyclovir had complete resolution or clinical improvement, respectively, of their HSV infection-related longitudinal ulcers. The currently reported patient's cutaneous HSV infection-associated ulcers developed while he was receiving 1000mg of valacyclovir twice daily; since an acyclovir-resistant HSV infection had previously been documented, the initial therapy of intravenous acyclovir was changed to intravenous foscarnet with subsequent clinical improvement of his skin lesions.

The described patient in this report has some unique characteristics with regard to his disseminated HSV-1 skin infection. He is the first man in whom the cutaneous HSV infection-associated linear erosions demonstrating the "knife-cut sign" are described. His clinical lesions of HSV infection also expand the sites of involvement of the "knife-cut sign" to include the curved fold created in the supra-auricular area between the ear and the scalp. It is reasonable to postulate that in an immunocompromised patient with cutaneous HSV infection, any intertriginous areas or naturally occurring body fold (such as the anterior or posterior neck, the antecubital fossa, or the popliteal fossa) may be susceptible to developing linear erosive virus-related skin lesions.

CONCLUSION

The "knife-cut sign" is a distinctive presentation of cutaneous HSV infection in immunocompromised patients. This form of HSV infection in immunosuppressed individuals may indeed be more common—yet under recognized—than the paucity of reported patients in the literature suggests.[10] Morphologically, the viral-associated skin lesions appear as deep linear ulcers and fissures in intertriginous areas, such as the folds in the inguinal area, the vulva, and the abdomen. Other reported sites include beneath the breast, within the gluteal cleft, and the area between the ear and the scalp. The patients whose HSV infection has "knife-cut" clinical lesions are immunosuppressed secondary to either an underlying medical condition or a systemic therapy or both. HSV-1 and HSV-2 have been observed as the causative viral serotype; however, HSV-1 has been associated with genital and inframammary lesions in addition to virus-related skin lesions above the neck. Direct fluorescent antibody testing is a rapid method for confirming the clinically suspected viral infection; however, false-negative results in two of five patients prompts consideration to also perform viral cultures and possibly lesional skin biopsies to establish the diagnosis. Systemic antiviral therapy should be initiated once the diagnosis is considered and maintained until the HSV infection-related skin lesions have resolved.

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